REMARKS

Claims 1-12 and 15-17 are pending. Applicants have cancelled claims 16 and 17 without prejudice and added new claims 18-28. Claims 1-12, 15, and 18-28 will therefore be pending upon entry of the proposed amendments.

I. Brief Overview of Claim Amendments and New Claims

Applicants have amended claim 1 as originally filed to address all rejections raised under 35 U.S.C. § 112, first and second paragraphs in the present Office Action. New claim 18, which depends from claim 1, is directed to compounds in which G^1 is optionally substituted phenyl. New claims 19-28, all of which depend from new claim 18, include the subject matter of claims 2-6; and presently amended claims 7, 9, 11, 12, and 15.

II. Detailed Summary of Claim Amendments and New Claims

[A] Applicants have amended claim 1 as follows.

[1] Applicants have amended the definition of G^1 to address the outstanding 35 U.S.C. § 112, second paragraph rejections. More specifically, Applicants have replaced the first three G^1 definition clauses with the following text:

> G^1 is a monocyclic ring structure of up to 7 ring atoms, which is selected from cycloalkyl; cycloalkenyl; heterocycloalkyl; unsaturated heterocycloalkyl; aryl; or an aromatic heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N; each of which is optionally substituted by one or more substituents independently selected from halogen, hydroxy, CHO, C1 to 6 alkyl, C1 to 6 alkoxy, halo-C1 to 6 alkoxy, amino, N-alkylamino, N,N-dialkylamino, alkylsulfonamino, C2 to 6 alkanoylamino, cyano, nitro, mercapto, alkylthio, alkylsulfonyl, alkylaminosulfonyl, C2 to 6 alkanoyl, aminocarbonyl, N-alkylamino-carbonyl, N,N-amino-carbonyl; wherein any alkyl radical within any substituent may itself be optionally substituted with one or more groups selected from halogen, hydroxy, C1 to 6 alkoxy, halo-C1 to 6 alkoxy, amino, N-alkylamino, N,N-dialkylamino, N-alkylsulfonamino, N-C2 to 6 alkanoylamino, cyano, nitro, mercapto, alkylthio, alkylsulfonyl, N-alkylaminosulfonyl, CHO, C2

to 6 alkanoyl, aminocarbonyl, N-alkylaminocarbonyl, and N,N-dialkylaminocarbonyl; and wherein any alkyl radical is a C1 to 6 alkyl radical; or

G^1 is a bicyclic ring structure, wherein each ring in the bicyclic ring structure is, independently, a ring of up to 7 ring atoms, wherein each ring in the bicyclic ring structure is, independently, selected from cycloalkyl; cycloalkenyl; heterocycloalkyl; unsaturated heterocycloalkyl; aryl; or an aromatic heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N; wherein each ring in the bicyclic ring structure is, independently, optionally substituted by one or more substituents independently selected from halogen, hydroxy, CHO, C1 to 6 alkyl, C1 to 6 alkoxy, halo-C1 to 6 alkoxy, amino, N-alkylamino, N,N-dialkylamino, alkylsulfonamino, C2 to 6 alkanoylamino, cyano, nitro, mercapto, alkylthio, alkylsulfonyl, alkylaminosulfonyl, C2 to 6 alkanoyl, aminocarbonyl, N-alkylamino-carbonyl, N,N-amino-carbonyl; wherein any alkyl radical within any substituent may itself be optionally substituted with one or more groups selected from halogen, hydroxy, C1 to 6 alkoxy, halo-C1 to 6 alkoxy, amino, N-alkylamino, N,N-dialkylamino, N-alkylsulfonamino, N-C2 to 6 alkanoylamino, cyano, nitro, mercapto, alkylthio, alkylsulfonyl, N-alkylaminosulfonyl, CHO, C2 to 6 alkanoyl, aminocarbonyl, N-alkylaminocarbonyl, and N,N-dialkylaminocarbonyl; and wherein any alkyl radical is a C1 to 6 alkyl radical; or

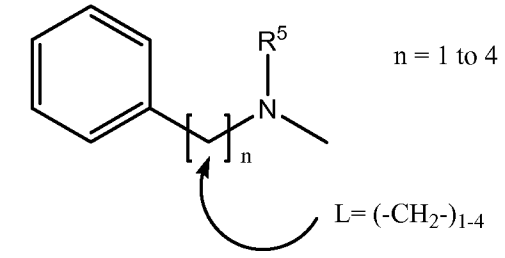
G^1 is a tricyclic ring structure, wherein each ring in the tricyclic ring structure is, independently, a ring of up to 7 ring atoms, wherein each ring in the tricyclic ring structure is, independently, selected from cycloalkyl; cycloalkenyl; heterocycloalkyl; unsaturated heterocycloalkyl; aryl; or an aromatic heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N; wherein each ring in the tricyclic ring structure is, independently, optionally substituted by one or more substituents independently selected from halogen, hydroxy, CHO, C1 to 6 alkyl, C1 to 6 alkoxy, halo-C1 to 6 alkoxy, amino, N-alkylamino, N,N-dialkylamino, alkylsulfonamino, C2 to 6 alkanoylamino, cyano, nitro, mercapto, alkylthio, alkylsulfonyl, alkylaminosulfonyl, C2 to 6 alkanoyl, aminocarbonyl, N-alkylamino-carbonyl, N,N-amino-carbonyl; wherein any alkyl radical within any substituent may itself be optionally substituted with one or more groups selected from halogen, hydroxy, C1 to 6 alkoxy, halo-C1 to 6 alkoxy, amino, N-alkylamino, N,N-dialkylamino, N-alkylsulfonamino, N-C2 to 6 alkanoylamino, cyano, nitro, mercapto, alkylthio, alkylsulfonyl, N-alkylaminosulfonyl, CHO, C2 to 6 alkanoyl, aminocarbonyl, N-alkylaminocarbonyl, and N,N-dialkylaminocarbonyl; and wherein any alkyl radical is a C1 to 6 alkyl radical; or

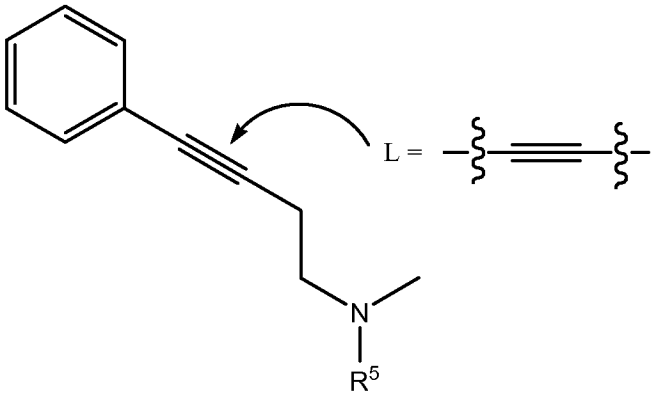
G^1 is a tetracyclic ring structure, wherein each ring in the tetracyclic ring structure is, independently, a ring of up to 7 ring atoms, wherein each ring in the tetracyclic ring structure is, independently, selected from cycloalkyl; cycloalkenyl; heterocycloalkyl; unsaturated heterocycloalkyl; aryl; or an aromatic heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N; wherein each ring in the tetracyclic ring structure is, independently, optionally substituted by one or more substituents independently selected from halogen, hydroxy, CHO, C1 to 6 alkyl, C1 to 6 alkoxy, halo-C1 to 6 alkoxy, amino, N-alkylamino, N,N-dialkylamino, alkylsulfonamino, C2 to 6 alkanoylamino, cyano, nitro, mercapto, alkylthio, alkylsulfonyl, alkylaminosulfonyl, C2 to 6 alkanoyl, aminocarbonyl, N-alkylamino-carbonyl, N,N-amino-carbonyl; wherein any alkyl radical within any substituent may itself be optionally substituted with one or more groups selected from halogen, hydroxy, C1 to 6 alkoxy, halo-C1 to 6 alkoxy, amino, N-alkylamino, N,N-dialkylamino, N-alkylsulfonamino, N-C2 to 6 alkanoylamino, cyano, nitro, mercapto, alkylthio, alkylsulfonyl, N-alkylaminosulfonyl, CHO, C2 to 6 alkanoyl, aminocarbonyl, N-alkylaminocarbonyl, and N,N-dialkylaminocarbonyl; and wherein any alkyl radical is a C1 to 6 alkyl radical;

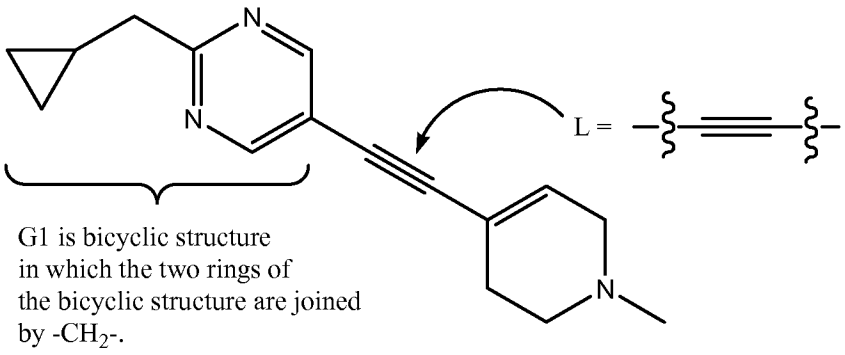
As can be seen, the G^1 definition no longer recites "comprising," "thiol" (replaced with "mercapto," which is an art-recognized term used to describe the characteristic " -SH" functional group that is present in a thiol), or "carbamate." Further clarification is provided in the remarks below with regard to "alkylsulfonamino." Support for these amendments can be found throughout the specification, e.g., page 9, lines 15-25; page 13; page 14, lines 4-8; and claim 1 as originally filed.

[2] Applicants have also amended the definition of L and the penultimate G^1 definition clause (i.e., the clause beginning with "and when G^1 is a bicyclic") to address the outstanding 35 U.S.C. § 112, second paragraph rejections. More specifically, Applicants have inserted "divalent" before each of the following terms in the definition of variable "L:" C2 to 6 alkynyl, C2 to 6 alkenyl, C1 to 6 alkyl, C1 to 6 heteroalkyl and C3 to 6 heteroalkynyl. Similarly, Applicants have inserted "divalent" before each of the following terms in the penultimate G^1 definition clause: C1-6 alkyl, C1-6 haloalkyl, C1-6 heteroalkyl, C2-6 alkenyl, and C2-6 alkynyl. Support for these amendments can be found throughout the specification, e.g., at page 11, lines

11-16 (which specifically discloses examples of divalent "C1 to 6 heteroalkyl" and divalent "C3 to 6 heteroalkynyl"); and page 13-- see, e.g., the three exemplary (and non-limiting) G^1-L-Y-$N(R^5)$- fragments shown below:







[3] Finally, Applicants have deleted the phrase "or solvate."

[B] Applicants have amended claims 7 and 9-12 to be consistent with claim 1 as presently amended. Applicants have amended claim 15 to depend from claim 1 instead of claim 17. As such, Applicants have also incorporated some of the wording from claim 17 as originally filed. Support for new claim 18 can be found throughout the specification, e.g., at page 9, lines 15-18. New claims 19-28, all of which depend from new claim 18, include the subject matter of claims 2-6; and presently amended claims 7, 9, 11, 12, and 15.

[C] The foregoing amendments, which introduce no new matter, are being made for the sole purpose of expediting prosecution of the present application; and Applicants expressly reserve the right to pursue any cancelled subject matter in one or more continuing applications.

Rejections under 35 U.S.C. § 112, first paragraph

I. Claims 15-17 are rejected for allegedly failing to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. The rejection of claims 16 and 17 is moot in view of the cancellation of these claims.

Claim 15 as presently amended is directed to a "method of treating asthma or chronic obstructive pulmonary disease, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in claim 1." For ease of exposition, "chronic obstructive pulmonary disease" will be referred to in the discussion below by the art-recognized acronym "COPD."

Applicants respectfully request reconsideration and withdrawal of the rejection in view of the following remarks.

[A] The Federal Circuit discussed the purpose of the enablement requirement of 35 U.S.C. § 112, ¶1 in *Warner-Lambert Co. v. Teva Pharmaceuticals USA, Inc.* 418 F.3d 1326, 1336-1337 (2005) (underline emphasis added):

> The purpose of this requirement is to ensure that 'the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims.' *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195-96 (Fed.Cir.1999); see also Donald S. Chisum, 3 Chisum on Patents § 7.01 (2002).

The Federal Circuit in *Warner-Lambert* stressed that the specification must teach one how to make and use the claimed invention without undue experimentation (*Id.* at 1337, emphasis added):

> Accordingly, we have held that the specification must provide sufficient teaching such that one skilled in the art could make and use the full scope of the invention without undue experimentation. *[citations omitted]* 'The key word is 'undue,' not experimentation.'' *Wands*, 858 F.2d at 737 (citation omitted). That is, the specification need only teach those aspects of the invention that one skilled in the art could not figure out without undue experimentation. See, e.g., *Nat'l Recovery Techs.*, 166 F.3d at 1196 ('The scope of enablement ... is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation.'); *Wands*, 858 F.2d at 736-37 ('Enablement is not precluded by the necessity for some experimentation such as routine screening.').

[B] The specification teaches a genus of triazolone-containing compounds that can inhibit one or more metalloproteinase enzymes (e.g., MMPs, e.g., MMP9 and MMP12).

[1] The specification teaches one how to synthesize the claimed compounds and provides guidance for determining a regimen for administering the claimed compounds to patients (see specification at page 18, line 11 through page 23, line 5; and the numerous synthesis examples beginning at page 24). The Office's comments regarding "dosage" and "regimen" is noted. The selection of the actual dosages is within skill of the art and may be readily determined based on the physical profile of the subject and guided, for example, by clinical results conducted under the auspices of Food and Drug Administration review. In any event,

information that is known to persons of ordinary skill in the art need not be included in the Specification. See *In re Buchner* 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). In other words, with the information in the Specification, one of ordinary skill in the art can work out appropriate dosages, formulations, and routes of administration.

[2]

The specification provides art recognized assays that can be used to evaluate the claimed compounds' ability to inhibit metalloproteinase enzyme (e.g., MMP) activity.

In addition, the specification provides biological data, which not only show that the claimed compounds are relatively potent MMP inhibitors, but also demonstrate that the claimed compounds are relatively **specific** MMP inhibitors, showing specificity for, e.g., MMP9 and MMP12. These data are discussed in more detail below.

The table at the bottom of page 40 of the specification shows IC_{50} values exhibited by three compounds that are encompassed by claim 1 and exemplified in the specification (the compound of example number **4** is also encompassed by new claim 18). IC_{50} values are inhibitory concentrations. Qualitatively, the IC_{50} for a substance (e.g., a drug) is a measure of the substance's effectiveness in inhibiting a particular biological process. Quantitatively, the IC_{50} for a substance is the concentration of the substance needed to inhibit the particular biological process by 50%. The IC_{50} values reported in the table at the bottom of page 40 of the specification indicate the concentration (nanomolar) of claimed compound at which 50% of the inhibitory effect on the indicated MMP. As can be seen, each of the three compounds exhibited IC_{50} values in the nanomolar (and in several instances in the low nanomolar) range when tested MMP9 and MMP12. Thus, this data demonstrate that the claimed compounds are relatively potent and relatively specific inhibitors of MMP9 and MMP12.

[C]

Metalloproteinase enzymes (e.g., MMPs) were known in the art as of Applicants' filing date. Also available were assays for evaluating a chemical compound's ability to inhibit metalloproteinase enzyme (e.g., MMP) activity and treat various metalloproteinase enzyme (e.g., MMP) related disorders and conditions.

Moreover, the **nexus** between (1) MMP inhibition and (2) COPD and asthma and the management of these disorders and conditions had also been established (and arguably well established) as of Applicants' filing date. This is discussed in detail in the Background section of the specification, e.g., at page 2, lines 14-29; and page 4, lines 4-10 (emphasis added):

> MMP12, also known as macrophage elastase or metalloelastase, was initially cloned in the mouse by Shapiro *et al* [1992, Journal of Biological Chemistry 267: 4664] and in man by the same group in 1995. MMP12 is preferentially expressed in activated macrophages, and has been shown to be secreted from alveolar macrophages from smokers [Shapiro *et al*, 1993, Journal of Biological Chemistry, 268: 23824] as well as in foam cells in atherosclerotic lesions [Matsumoto *et al*, 1998, Am J Pathol 153: 109]. A mouse model of COPD is based on challenge of mice with cigarette smoke for six months, two cigarettes a day six days a week. Wild-type mice developed pulmonary emphysema after this treatment. **When MMP12 knock-out mice were tested in this model they developed no significant emphysema, strongly indicating that MMP12 is a key enzyme in the COPD pathogenesis**. The role of MMPs such as MMP12 in COPD (emphysema and bronchitis) is discussed in Anderson and Shinagawa, 1999, Current Opinion in Anti-inflammatory and Immunomodulatory Investigational Drugs 1(1): 29-38. It was recently discovered that smoking increases macrophage infiltration and macrophage-derived MMP-12 expression in human carotid artery plaques Kangavari [Matetzky S, Fishbein MC *et al.*, Circulation 102:(18), 36-39 Suppl. S, Oct 31, 2000]. …
>
> **MMP9 release, measured using enzyme immunoassay, was significantly enhanced in fluids and in AM supernantants from untreated asthmatics compared with those from other populations** [Am. J. Resp. Cell & Mol. Biol., Nov 1997, 17 (5):583-591]. Also, increased MMP9 expression has been observed in certain other pathological conditions, thereby implicating MMP9 in disease processes such as COPD, arthritis, tumour metastasis, Alzheimer's, Multiple Sclerosis, and plaque rupture in atherosclerosis leading to acute coronary conditions such as Myocardial Infarction.

Applicant note that the Federal Circuit in *Callicrate v. Wadsworth Mfg., Inc.* 427 F.3d 1361, 1374 (2005) held that the **background** section of a patent specification can enable a feature of a claimed invention: "First, a patent specification may sufficiently enable a feature under § 112, ¶ 1, even if only the background section provides the enabling disclosure."

[D] Thus, Applicants have shown that the claimed compounds inhibit MMPs (e.g., MMP9 and MMP12) *in vitro* and submit that in view of the **nexus** between (1) MMP inhibition and (2) COPD and asthma, the foregoing data constitute working examples of the claimed methods. See MPEP 2164.02, which provides, in part:

> The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).
>
> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):
>
> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

Applicants submit there is a reasonable correlation between the MMP inhibitory activity exhibited by the claimed compounds in the aforementioned *in vitro* assays and *in vivo* activity. As such, the skilled artisan, at the time of filing, would therefore have reasonably predicted that the claimed compounds would have been useful for treating COPD and asthma-- one can enable a claim of treating the claimed cancers without having FDA approval or clinical acceptance of the method.

[E] The Federal Circuit in *In re Wright* 27 USPQ2d 1510, 1513 (1993) discussed the requirements for rejecting a claim under the enablement requirement of 35 U.S.C. § 112, first paragraph (emphasis added):

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement.

Applicants submit that the Office has not met this burden because, at the very least, the Office has not identified any aspect of the claimed methods that a person of ordinary skill in the art "could not figure out without undue experimentation" (*Warner-Lambert Co. v. Teva Pharmaceuticals USA, Inc.* 418 F.3d 1337). There is indeed an established link between MMP inhibition and COPD and asthma. Further, the skilled artisan could evaluate the ability of Applicants' claimed compounds to treat COPD or asthma by synthesizing a candidate compound of the claims and subjecting that compound to an art-recognized assay for treating COPD or asthma, respectively. In other words, the specification provides sufficient teaching such that a person of ordinary skill in the art could practice the claimed methods without undue experimentation.

Of course, this is **not** to say that the specification does not establish a nexus between the instantly claimed compounds and the treatment of COPD and asthma. Rather, establishing the

nexus apparently sought by the Office falls within the purview of routine screening, which in and of itself does not preclude enablement (*see Wands*, 858 F.2d at 736-37).

In view of the foregoing, Applicants respectfully request that the rejection be reconsidered and withdrawn.

II. Claims 3 and 9 are rejected for allegedly failing to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. The recitation of "solvate" in these claims appear to be the basis for the rejection (see pages 8-9 of the Office Action).

Applicants respectfully disagree with the grounds for the rejection; however, to expedite prosecution of the present application, Applicants have deleted all occurrences of " solvate" from the present claims. In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-8, 10-12, and 15-17 are rejected under 35 U.S.C. § 112, second paragraph on various grounds for allegedly being indefinite.

[A] The rejection states, in part (Office Action, page 9, emphasis added):

> Because L is required to be a **divalent** moiety, the monovalent groups (C2 to 6 alkynyl, C2 to 6 alkenyl, C1 to 6 alkyl, C1 to 6 heteroalkyl or C3 to 6 heteroalkynyl) cannot represent this variable.

The Office Action contains a similar statement concerning the recitation of the moieties listed above in the definition of groups joining two or more constituent rings in a G^1 bicyclic, tricyclic, or tetracyclic ring structure (see page 10 of Office Action).

Applicants respectfully disagree with the grounds for the rejection; however, to expedite prosecution of the present application, Applicants have inserted "divalent" before each of the following terms in the definition of variable "L:" C2 to 6 alkynyl, C2 to 6 alkenyl, C1 to 6 alkyl, C1 to 6 heteroalkyl and C3 to 6 heteroalkynyl. Similarly, Applicants have inserted "divalent"

before each of the following terms in the penultimate G^1 definition clause: C1-6 alkyl, C1-6 haloalkyl, C1-6 heteroalkyl, C2-6 alkenyl, and C2-6 alkynyl.

[B] The recitation of "sulfonamino," "thiol," and "carbamate" also appear to form basis for the rejection (Office Action, page 9).

Applicants respectfully disagree with the grounds for the rejection; however, to expedite prosecution of the present application, Applicants have replaced "thiol" with "mercapto," which is an art-recognized term used to describe the characteristic " -SH" functional group that is present in a thiol; and deleted "carbamate."

Applicants respectfully point out that the present application does not disclose "sulfonamino" in isolation. Rather, only the term "alkylsulfonamino" is used, which to the best of Applicants' knowledge, is the correct nomenclature to describe a moiety "alkyl-SO_2-N<."

[C] The rejection states, in part, with regard to variable G1 (Office Action, page 9):

> It is not possible to determine the number of ring structures and/or whether they are attached to each other or substituents of each other.

Applicants respectfully disagree with the grounds for the rejection; however, to expedite prosecution of the present application, Applicants have replaced the first three G^1 definition clauses with a definition that does not recite "comprising" and further clarifies that G^1 is a monocyclic ring structure (1 ring *in toto*), a bicyclic ring structure (2 rings *in toto*), a tricyclic ring structure (3 rings *in toto*), or a tetracyclic ring structure (4 rings *in toto*). The amended G^1 definition further clarifies the size and nature of the each constituent ring as well as the substitutents (none of which are cyclic groups) that can be present thereon.

The Applicant is permitted to be his or her own lexicographer, and the present application clearly defines what Applicants intended terms such as "bicyclic" to mean. Using "bicyclic" as an example, the skilled artisan would understand this term to mean a ring structure having 2 rings *in toto* , the two rings either **(i)** being joined by a bond, an atom, or a group of atoms (i.e., one ring atom in each of the two rings serving as a connection point for the joinder bond, atom,

or group of atoms); or **(ii)** being fused to one another. See specification, e.g., at page 9, lines 15-25 and page 14, lines 4-8.

As such, the skilled artisan reading the present claims in conjunction with the specification would understand the scope of G^1, and hence the metes and bounds of the present claims.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection under 35 U.S.C. § 102

Claims 1, 3, 4, 6, 8, 11, 12, and 16 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Ikeura, et al., WO 03/101964 ("Ikeura").

This is respectfully traversed. The Office relies on the disclosure of "RN632352-46-6" (Office Action, page 10) in Ikeura. As acknowledged by the Office, the part of the molecule in RN632352-46-6 that corresponds to Applicants' G^1 includes a tetrazole ring, which is an aromatic heterocyclic ring containing **4** heteroatoms (nitrogen). In contrast, the present claims require that when G^1 includes an aromatic heterocyclic ring, it can include at most only **3** heteroatoms. As such, RN632352-46-6 in Ikeura falls outside of the scope of the present claims. Ikeura therefore does not anticipate the present claims. In view of the foregoing, Applicants respectfully request that the rejection be reconsidered and withdrawn.

CONCLUSION

The fee in the amount of $1,110 for the three month extension fee is being paid concurrently herewith on the Electronic Filing System (EFS) by way of a Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 06275-522US1 / 101414-1P US.

Respectfully submitted,

Date: November 21, 2008

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